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Editorial

Quantitative neurosymptomatics; linking quantitative biology to neuropsychiatry

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The treatment of neuropsychiatric disorders currently relies on over 100 compounds but it is still far from being satisfactory regarding tolerability and, even more, efficacy given the high rate of partial or no benefit at all particularly in Schizophrenia and Alzheimer Disease. In fact, after over 50 years from the discovery of the first antidepressant and antipsychotic drugs, their mechanism of action still mainly relies upon the modulation of dopaminergic and serotonergic systems for psychiatric disorders and of acetylcholine for cognition. The benefits of these classes of compounds should not be underestimated but neither should their shortcomings, the number of patients that do not respond, nor the areas of clinical unmet need that current therapies do not even attempt to tackle. Few new mechanisms of action have been identified in the last decades. *Paralleling, this innovative deceleration in the identification of novel therapeutic approaches our diagnostic framework has also only gone through a limited evolution over this same time-period. Despite many significant advances, in quantitative neuroscience, clinical practice is still based principally on a qualitative assessment of perceived symptoms.* It is clear therefore that we need a paradigm shift to rekindle the drug discovery process and facilitate better matching of patient to therapeutic. A number of projects have been recently proposed in order to innovate the field (see for example NEWMEDS (Artigas et al., 2017)), but converging evidence, summarized in the first paper (Kas et al in this issue (Kas et al., 2017)) suggests the need for a more radical change of perspective. The core of this thesis is that the direction for innovation should focus on the biological systems that can be quantitatively demonstrated as being altered in disease. From this understanding new transdiagnostic hypotheses explaining the clinical deficits, independent from traditional categorical designations (O'Donnell and Ehlers, 2015) can be allowed to emerge.

Having relied entirely on a clustered symptomatic classification of neuropsychiatric illness there is much discussion currently, such as the RDoC (Cuthbert, 2018) and ROAMER initiative (Haro et al., 2014), as to whether a more pragmatic quantitative biology approach may now be achievable. Converging evidence is in fact suggesting that we are close to the point of achieving this goal. As a consequence the transdiagnostic approach is gaining adherents in many areas and hence triggering novel experimental proposals (Bipolar Disorder and Schizophrenia Working Group of the Psychiatric

Genomics Consortium., 2018)(Kas et al., 2007). Amongst these an industry consortium came together in 2014 and working *through* the Innovative Medicine Initiative (IMI) developed a call based on the emergence of the much improved ability to integrate imaging, electrophysiological, cognitive, genetic and real world parameters. This advent being viewed as an opportunity to bring a quantitative biological approach to the classification and understanding of this complex area. In particular, the call looked to determine whether similar symptomatologies, that are assumed to result from different pathological processes, could be dissociated using quantitative parameters. The identification of homogeneous subgroups of subjects sharing similar pathophysiological mechanisms may then facilitate; the discovery of innovative treatments, offer improved stratification of patients providing improved alignment of the best drug in the right patient as well as more rational clinical trial design, and in turn influence also regulatory processes (Tome and Isaac, 2018). From an academic perspective a biologically based clinical understand also offers dramatic improvements in our ability to reverse translate effectively into the pre-clinical milieu.

The PRISM project (Psychiatric Ratings using Intermediate Stratified Markers), which developed from this call, has taken the theme of Social Withdrawal as the symptomatic dimension while schizophrenia and Alzheimer's dementia provide the two differing pathologies which share this deleterious symptomatic dimension (<https://prism-project.eu>). In view of this symptomatic dimension, William Carpenter has provided a commentary manuscript for this special issue focusing on clinical concepts and the relevance of social engagement in psychopathology (Carpenter, 2017). The PRISM project aims to provide new classification tools focusing on the two main neuropsychiatric disorders based on quantitative biological parameters. This will be based on a deep phenotyping assessment in newly recruited subjects covering social withdrawal, attention, sensory processing, and working memory versus digital, brain imaging, EEG and epigenetic biomarkers. In addition, a cross-disorder genome-wide genetic analysis will be performed in the largest worldwide available cohorts of patients with the aim to identify shared genetic factors related to the common social withdrawal symptoms in these disorders. Furthermore, a preclinical platform will be implemented to *allow back translation from* human findings into rodents to facilitate studies to further our understanding of neurobiological substrates underlying the identified clinical and biologically meaningful quantitative parameters. For example, as was addressed by Hornix et al in this issue, studies on the combined analyses of neural circuit development and functioning will become necessary to expand our understanding of sensory processing and behavioural deficits that are relevant across the neuropsychiatric spectrum (Hornix et al., 2018).

The manuscripts presented in this special issue review the pertinent literature and detail the concept from a variety of perspectives. The first paper (Kas et al in this issue (Kas et al., 2017)) addresses the background to the arguments in favour of a quantitative as opposed to a purely symptomatic approach in this area, the potential benefits if successful, and a broad brush outline as to how it is planned to achieve this goal. Specifically, this involved identifying, what turned out to be, four key areas for analysis. Porcelli and colleagues (Porcelli et al., 2018) then lay out a comprehensive account of the current understanding of the neurobiology of social withdrawal that provides the foundation for the rest of the project. The innovative nature of this review is to combine existing evidence about neurobiology of social withdrawal in a way that makes clear how its determinants are, at least in part, independent from the clinical diagnosis of the subject. Moreover, determinants have been studied in previous human and animal studies but never combined in a unitary interrelated mechanism of action, which is presented in the paper. This model will constitute the working

hypothesis to be tested within the project. From these starting points the structure of the clinical recruitment work was devised based upon an assessment of the four key areas of research within the clinical study protocol (Bilderbeck in this issue (Bilderbeck et al., 2018)). These four key areas are: social withdrawal itself (Van der Wee, et al in this issue (van der Wee et al., 2018)), sensory processing (Danjou, et al in this issue (Danjou et al., 2018)), as well as attention and working memory (Gilmour, et al in this issue[MK1]) identified by the teams initial review. Furthermore, the potential for back translation of human findings using homologous paradigms in rodents is then reviewed in detail (Hengerer in this issue[MK2]). These areas also share the key attribute that we believe they are robust and deliverable within the practical constraints of the resources available to the project. There are though other areas that have transdiagnostic relevance in this area. A good example of this are sleep disturbances. In this issue Winsky-Sommerer et al aware of the PRISM initiative have taken this transdiagnostic perspective to review whether sleep; its quality, timing and structure, could be another rich vein to explore if certainly technical challenges can be addressed (Winsky-Sommerer et al., 2018).

The material included in this issue it is hoped will therefore inform the reader about the background and evidence of a potentially fruitful improvement in the understanding of neuropsychiatric disorders based on quantitative biological parameters possibly leading to more effective clinical and pre-clinical research and drug discovery. Further, should this approach prove fruitful our need to review the literature across traditional classifications will become vital. These reviews may therefore provide a template for this novel perspective while also retaining a pragmatic realism derived from the technical challenges of such transdiagnostic approaches.

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